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| KELLY, ROBERT M | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/618,299 | BARSOUM ET AL. | |
| | Examiner | Art Unit | |
| | Robert M. Kelly | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,34-39,41-44,46 and 52-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,34-39,41-44,46 and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response and amendments of 8/4/06 has been entered.

Claims 1, 34, 36-37, 44, and 52 have been amended.

Claims 45 and 47-49 have been cancelled.

Claims 1, 34-39, 41-44, 46, and 52-54 are presently pending and considered.

### *Claim Status, Cancelled Claims*

In light of Applicant's cancellation of claims 45 and 47-49, all objections and/or rejections of such claims are rendered moot, and thus are withdrawn.

### *Note: Submission of Art Without IDS*

It is noted that Applicant has submitted several non-patent literature articles, without providing an IDS. These have been put in the file but not formally been made of record, and only considered to the extent necessary to respond to Applicants' arguments.

### *Claim Rejections - 35 USC § 112 – clarity*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 38 recites the limitation "said viral vector is an adenovirus vector" in Claims 34-37. There is insufficient antecedent basis for this limitation in the claim. Specifically, it is clear in the cited parent claims that the agent may also be a viral vector, hence, it is unclear which viral vector is referring to.

Claim 44 recites the limitation "said viral vector" in Claims 34-37. There is insufficient antecedent basis for this limitation in the claim. Specifically, it is clear in the cited parent claims that the agent may also be a viral vector, hence, it is unclear which viral vector is referring to.

Claim 46 recites the limitation "said viral vector" in Claims 34-37. There is insufficient antecedent basis for this limitation in the claim. Specifically, it is clear in the cited parent claims that the agent may also be a viral vector, hence, it is unclear which viral vector is referring to.

***Claim Rejections - 35 USC § 112 – new matter***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 34-36, 38-39, 41-44, 46, and 52-54 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims encompass the exclusion of agents which are identical to the viral vector comprising the transgene, and as not being administered simultaneously, and wherein agents that are identical to the vector comprising the transgene being administered prior to the viral vector.

However, the Examiner has searched the specification and claims as originally-filed, and found no explicit or implicit support **for a general exception to any agent used set forth in**

**Applicant's claim amendment**, except that found in the examples, drawn to a specific administration to a specific animal, at specific times, and as such, such embodiments to the identical vector must be drawn to the same method and materials as the examples, as such support is implicit.

Moreover, while Applicant avers that support is found at various passages in the specification, the Examiner has no such support in the cited passages (Applicant's argument of 8/4/06, p. 9, last paragraph.

Hence, these claims are rejected for comprising new matter.

***Claim Rejections - 35 USC § 112 – written description***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 34-39, 41-44, 46, and 52-54 remain and/or are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons necessitated of record, as modified below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims encompass a generic agent that reduces a generic Kupffer cell function, may be a generic viral vector, or a generic particle with a size of about 10-1000nm.

The specification discloses broadly that a generic agent that saturates the viral uptake capacity of kupffer cells can be used (p. 3, paragraph 1). However, this is in the context of Applicant's finding that low doses of adenoviruses can result in increased expression of subsequently, or concurrently delivered, adenovirus comprising a transgene (p. 2, paragraph 2). The mechanism of such adenoviral action is not understood by Applicant, as they do not wish to be bound by any theory (Id., paragraph 3). Moreover, Applicant envisions the other already-known agents that deplete the amount of kupffer cells (p. 3,paragraph 3). However, Applicant has not demonstrated any other generic agent aside from the adenoviral vector and those already known in the art to bring about the effect desired. In fact, Applicant's particle size range appears to be drawn from the size of adenoviral particles and the small chemicals already known to work. However, these generic characteristics, i.e., being another virus or being of the size of the virus used, or the size of chemicals known in the art would not be something the Artisan would understand to be related in a cause and effect relationship, rather, they are general characteristics of the individual entities. Moreover, no art of record demonstrates that any other agent could produce similar effects. Hence, Applicant did not possess a generic agent that reduces a generic Kupffer cell function. In fact, it would appear that a generic Kupffer cell function is nothing that is wished to be effected, but instead, the Artisan would only envision the function desired to be effected is the uptake of a subsequently delivered virus, which is what Applicant has envisioned, but does not appear to possess. Further, the particle sizes appear to encompass various cytotoxins which Applicant has also presented evidence of in the art, however, a compound within Applicant's size range would not be considered a "particle" but a chemical compound. Particulate matter is not generally understood by the Artisan to be a soluble chemical compound.

To put this in terms the layman can understand: the USPTO issues a patent, with the right to preclude others from practicing the invented subject matter only if the Artisan (and therefore also the USPTO) understands what subject matter is encompassed, and such subject matter meets the other requirements for patentability. Such subject matter then, when the scope of structures encompassed is properly claimed and understood by the Artisan can then be properly issued, provided the other requirements for patentability are met. However, if a material is not so-defined, either with structure, or with a function and an understanding of the structure required to obtain such function, then it is impossible to determine what subject matter infringes on Applicant's claimed subject matter.

Applicant's requirement of affecting a generic Kupffer cell function appears to have nothing to do with stopping the uptake of the adenoviral vectors by Kupffer cells, which is Applicant's only explanation of the understanding of what is required to be effected in the Kupffer cells, but further, as has been stated repeatedly, even Applicant admits they do not know the mechanism of such affects causing the increased transgene expression after administration of the vector. Therefore, beyond an understanding by Applicant that the effect can be accomplished with an adenoviral vector, the Artisan could not understand Applicant to have possessed any larger genera of an agent, except adenoviral particles and liposomally-encapsulated doxorubicin. Further, because the generic Kupffer cell function appears to be irrelevant beyond a mere declaration in the specification that it should work, there is also no structure to determine here, in fact the species which have the effect are broad, e.g., sugars could change the metabolism function of the cells, and such would appear to have no relevance to Applicant's invention: i.e., the Artisan would not understand sugars to have this effect.

Hence, the generic claiming of an agent which affects Kupffer cell function is not a genera which the Artisan would have understood Applicant to have been in possession of at the time of filing.

***Response to Argument – written description***

It is noted that the rejection has been changed and Applicant is enabled for a generic agent that reduces the levels of Kupffer cells, as it is well known in the art that liposome-encapsulated cytotoxic agents are preferentially taken up by Kupffer cells when administered intravenously, thereby killing those cells, and allowing increased gene transfer of subsequently delivered adenovirus (e.g., Wolff, et al. (1997) J. Virol., 71(1): 624-29). Hence, only relevant arguments are addressed below.

Applicant's argument of 8/4/06 has been fully considered but is not found persuasive.

Applicant argues that the law states that there is no requirement to demonstrate why or how an invention works, or even to understand or state the scientific principles behind the invention, and hence, Applicant is not required to describe the mechanism by which "an agent that reduces Kupffer cell function" works. In essence, Applicant argues that they teach how to achieve the claimed result, thereby satisfying the written description requirement (pp. 11-12).

Such is not persuasive. It is admitted that Applicant is not required to demonstrate they understand the mechanism by which the agent works, but in the absence of a mechanism, either in the Art or in Applicant's disclosure, the Artisan could not determine which agents are encompassed by the claims, and therefore, Applicant's claimed agents would be limited to those that Applicant has reduced to actual practice. This is because Applicant is claiming the agent by the function which it provides, and not a structure, and therefore, the Art could not properly be

searched by function, and the Artisan would not know what structures are encompassed by the Agents. To give an example, if the breadth of the claim were to be searched under Applicant's incorrect Application of the law, the Examiner would have to search the art for anything applied to a subject prior to the administration of any viral vector, and assert that the application of such agent is an agent under Applicant's claims absent reason to believe otherwise. Such is because we do not know if it is one of Applicant's agents. Similarly, those agents already applied in the art would be excluded from practice, because Applicant had obtained an incorrect patent for such applications.

Applicant argues that the Examiner's statement, regarding the breadth of viral vectors, particles and nucleic acids are without legal basis, as Applicant has demonstrated that they understand the scope of the vectors, particles and nucleic acids encompassed, and therefore, they have demonstrated possession.

Such is not persuasive. Similar to the above-made argument, while Applicant has demonstrated literal understanding of the genera and made the aversion that the genera will work, the Artisan nonetheless must be able to understand which members of the genera produce the effect desired as an agent which reduces such Kupffer function such that it causes the first viral vector to have increased expression. Hence, simple aversion that because they are a viral vector, or a particulate matter of the size range of those various species known to work, which, by the way, appear to work by distinct mechanisms (i.e., the small chemicals work by killing Kupffer cells, and the adenoviral vectors appear to quench the ability of the Kupffer cells to further absorb adenovirus subsequently administered), would not be understood by the Artisan to

be a property required, but simply a property (i.e., size or being a vector), of those agents known and/or shown to work.

Hence, the rejection is maintained and/or modified due to the amendments.

***Claim Rejections - 35 USC § 112 - enablement***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 34-39, 41-44, 46, 52-54 are and/or remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(i) a method for increasing the level of a therapeutic gene product in the liver of a subject, the method comprising administering to said subject a first adenoviral vector comprising a heterologous transgene encoding said therapeutic transgene product, operably linked to expression control elements for expression in hepatocytes and a second adenoviral vector that does not comprise said transgene, wherein said second adenoviral vector is administered prior to, or concurrently with, said first adenoviral vector, wherein the second adenoviral vector is administered intravenously, intraperitoneally, or directly to the liver;

(ii) a method for increasing the level of a therapeutic gene product in the liver of a subject, the method comprising administering to said subject a viral vector comprising a heterologous transgene encoding said therapeutic transgene product, operably linked to expression control elements for expression in hepatocytes and a liposome encapsulated cytotoxic agent, wherein said liposome encapsulated cytotoxic agent is administered prior to, or

concurrently with, said first adenoviral vector, wherein the liposome-encapsulated cytotoxic agent is administered intravenously, intraperitoneally, or directly to the liver;

(iii) a method for decreasing the filtration of an vector comprising a therapeutic transgene from the vascular system passing through the liver of a subject, comprising administering to a subject a first viral vector, and either (a) a second adenoviral particle vector or (b) a known kupffer cell cytotoxic agent, administered concurrently with, or prior to the first viral vector via the methods known to effect such killing of kupffer cells at the levels known to selectively affect kupffer cells, wherein the first viral vector enters the blood stream passing through the liver and the Kupffer cells to do not filter out such first viral vector and wherein further, if (a) is administered, the vector comprising the transgene is an adenoviral particle; and

(iv) a pharmaceutical composition comprising an adenovirus encoding a therapeutic gene product encoding a therapeutic transgene operably linked to expression

n control elements for expression in liver cells, and either (i) a second adenovirus not encoding such transgene, or (ii) a cytotoxin, and a pharmaceutically-acceptable carrier,

does not reasonably provide enablement for increasing gene product levels in any tissue other than liver, any agent for lowering any Kupffer cell function, any viral vector comprising the therapeutic transgene which is not an adenoviral particle comprising the therapeutic transgene when the agent is an adenoviral particle, any promoter, any agent which is not an adenovirus particle or cytotoxin, for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

***Note: misstated claims***

It is noted, as Applicant has shown, that Claims 1, 36-39, 41-49, and 52-54 were the properly-rejected claims in the prior official action (Applicant's argument of 8/4/06, p. 13, last paragraph).

***Note: new enabled embodiments***

The Examiner has included (iii), above, in order to make clear the differences between what Applicant appears to think is enabled, versus what they are claiming, however, it is noted that (iii) does appear to have issues of new matter, and Applicant does not claim such. Further, it is noted that new enablement includes a wider scope of agents that kill kupffer cells.

The bases of the rejection are reviewed below, for clarity of the record, followed by the response to Applicant's argument of 8/4/06.

Applicant's claimed invention encompasses any agent which lowers any Kupffer cell function, which encompasses any viral vector, including any nucleic acid encoding the minimal viral components, all cytotoxic agents, and any other agent, whether known or not, which lowers any Kupffer cell function. Further the claimed invention encompasses increasing transgene levels in any tissue, any promoter, and any method of administration of the viral vector encoding the transgene.

The claims are not enabled for the increased expression in any tissue because it is the Kupffer cells which are either killed by the cytotoxic agent, or sequestered somehow, by an unknown mechanism, by the administration of the first adenoviral particle. Such arguments are of record. Hence, by simply sequestering such cells, the subsequent administration of

adenoviruses are not as filtered by the Kupffer cells as they pass into the liver, allowing increased transformation of other cells. However, as has also been noted on the record, the other tissues are known to have macrophages, and it is not reasonably predictable that in any particular tissue that the vector would not be similarly filtered out, precluding action in such any other tissue. Moreover, Applicant has not claimed action on other macrophages, but action on Kupffer cells, hence, the claims are not enabled for any tissue. Further, as is noted above in (iii), Applicant has not claimed increased expression in other tissues by decreased filtration by Kupffer cells, allowing more virus to pass through the liver and affect other tissues, but instead they claim any form of administration, and therefore, the vast majority of embodiments would not pass through the liver before reaching the desired tissue. Hence, while Applicant may be enabled for the embodiment (iii), the Artisan would not understand Applicant to be claiming such embodiment from the teachings of the specification and the claimed subject matter. Hence, it would be undue experimentation to determine those tissues which would exhibit increased expression through any particular form administration of the vector encoding the transgene, amounting to inventing Applicant's claimed subject matter.

With regard to the promoter type, because the transgene expression could be increased in the liver tissues, the promoter would be required to be active in the liver cells, and not another tissue-specific type promoter.

With regard to the breadth of transgene-encoding vectors and agents, agents which are any particles of 10-1000 nm or agents which are any viral vector which is not an adenoviral particle, which are required to lower any Kupffer cell function, the only known agents are cytotoxins, and adenoviral particles, as is of record (e.g., Official Action of 7/29/05) and further

demonstrated by Applicant's submission of art demonstrating other cytotoxins used which are not encapsulated. It is noted throughout the record, the kupffer cell functions that are lowered are either (i) all functions due to killing by the cytotoxic agent which is uptaken due to being liposome encapsulated, or (ii) the ability to uptake adenovirus particles because of, presumably, being overburdened temporarily by the previous adenoviral particle administration. However, as is of record, it is further noted that Applicant admits that they do not know why the method works (e.g., SPECIFICATION, p. 2, paragraph 3). Hence, the relation between the function and the administered agent is not understood any better than that provided by the facts of record, and the Examiner cannot think of another reason, nor has the record provided any other reasoning. Hence, from the confluence of the Art and Applicant's disclosure, the Artisan would have to experiment to find the functions which could be lowered, and find the vector types and other compounds which could be used to lower functions, and then further experiment to determine if such administration allows for subsequent administration of any other vector type to exhibit increased expression in any particular tissue, even in the case of those compounds which inhibit other particles uptake as provided in the newly-submitted art, because the viruses enter through different mechanisms than that of the submitted art. Such necessarily amounts to undue experimentation, as it amounts to inventing the breadth of Applicant's claimed subject matter for Applicant.

Further, with regard to the various vector types carrying a transgene and particle sizes, the record is clear that adenoviral vectors can lower the action of kupffer cells to uptake further adenoviral vectors, at least temporarily, and further the record is clear that cytotoxins are uptaken by kupffer cells, thereby killing the kupffer cells, and therefore, temporarily lowering the

filtration of subsequent adenoviral particles by kupffer cells. These mechanisms are not, however, related such that any form of uptake of anything within the size range, will then disallow filtration by kupffer cells of any other vector type. To wit, while the kupffer cells are killed with the cytotoxin methods, and must regenerate before they can act again, and they are uptaken by a nonspecific method, the adenoviral particles act through natural mechanisms to enter the cells, through specific uptake via CAR and integrins. Applicant's proposal then that any form of nonspecific uptake will work is incorrect, as the only nonspecific uptake is one that kills the cells; however, particle size appears to be unrelated to the form of uptake by the viral particles. Moreover, while Applicant's specification proposes quenching of the ability to uptake adenovirus particle, and Applicant is not wishing to be bound by theory, and therefore does not know but only proposes that it stops all forms of viral vector uptake by kupffer cells, is not enough to overcome the fact that any other vector enters through other specific and/or non-specific mechanisms. Hence, even if the adenoviral vector agent filled up the mechanisms to uptake adenovirus, viral vectors that are not adenoviral are uptaken by another mechanism, e.g., by other receptors. Therefore, the Artisan would have to experiment to determine which particles agents, and which viral vector agents, may be used in combination with which viral vector comprising the therapeutic transgene, to affect decreased filtration by the kupffer cells. Such amounts to undue experimentation because it amounts to inventing Applicant's claimed subject matter.

With regard to uptake of cytotoxins, which are not encapsulated, those cytotoxins that are not selective for kupffer cells could not be administered by any other method than direct administration, otherwise the Artisan would predict that other cells than kupffer cells would be

killed, and further, for direct administration, the whole liver may be destroyed, killing the animal before the method could be accomplished.

***Response to Argument – Enablement***

Applicant's argument of 8/4/06 has been fully considered but is not found persuasive.

Applicant argues that the Examiner rejected the viral vectors encoding the transgene to be limited to those that enter the liver (p. 15).

Such is partially correct. The Examiner, as has been shown above, is further arguing that the kupffer cells are not reasonably predicted to have reduced sequestration of any form of viral vector when the adenovirus particle is used to reduce its function. Of course, if the kupffer cells are killed by the cytotoxic agent, it is natural that they cannot sequester anything. Hence, the enablement has been opened to include any vector type encoding the transgene when the liposome-encapsulated cytotoxin is used.

Applicant argues that many virus types are known to be taken up by Kupffer cells, and therefore, all the viruses can be used in the method to lower kupffer cell function (pp. 16-19).

Such is not persuasive. Applicant has not claimed the use of the same type of virus vector as that which encodes the transgene, but the use of any virus vector to inhibit sequestration of any other vector, and moreover, Applicant has not even explained how such would work. As is explained as simply as possible again (above) such is not reasonably predictable. Hence, it is undue experimentation to find those agents which are viral vectors, used in combination with other viral vectors which comprise the therapeutic transgene, which would affect the method.

Applicant argues that the breadth of viruses known to infect liver is wide, and therefore it is not undue experimentation to perform the breadth of these viruses encoding the transgene (pp. 19-20).

Such is partly persuasive, and hence, the breadth of enablement has been widened to use any virus vector with the liposome-encapsulated cytotoxin. However, as is explained above, with the use of another particle or agent, it is not reasonably predicted to work for any particular combination. Hence, it undue experimentation to find those combinations that work.

Applicant argues that it is well known that increasing the amount of a virus administered increases the amount of transformation of any particular tissue, and that by stopping sequestration of the liver's kupffer cells, such viral vectors encoding the transgene passing through the liver are increased, allowing for increased transformation, and therefore, the claims are enabled for any tissue (pp. 21-22).

Such is not persuasive. Applicant's claims do not require the viral vector transforming the tissue to pass through the liver, and further, the Art does admittedly demonstrate that increased transformation of tissues occurs with increased viral dose, but such is not what the Artisan would understand to be encompassed the claims, even though, the broad sense, they do encompass such because they do not specifically state any mechanisms whatsoever, which is why (iii) (above) was drafted. Applicant does not teach that these other tissues must be transformed specifically after passing through the liver, and therefore, the claims would not be understood to encompass such. If such is what Applicant wishes to claim, Applicant is requested to draft a claim to such subject matter. Further, the arguments to the combinations of agents and vectors still applies.

Applicant has perused that art and cited many more chemicals known to kill or inhibit the ability of kupffer cells to take up particulate matter, cited such art to the examiner, and argues

that they are enabled for more than liposome encapsulated cytotoxins, and further argue that it is not undue experimentation to determine what other compounds effect the method (pp. 23-25).

Such is partly persuasive. For those compounds that kill the kupffer cells however, it is not reasonably predictable that they could be administered by any method, as given above. Further, if directly administered and not selective only for kupffer cells, it is not reasonably predictable that the liver would not destroyed, thereby killing the subject, prior to the administration. Still further, for those that do not kill kupffer cells, the art does not demonstrate that adenoviral vectors, or any other vector type, would not be uptaken by the kupffer cells, and due to the fact that the mechanisms of action are clearly not known, but only suggested that the form of uptake is precluded, and due to the fact that viruses have different mechanisms of uptake, it is not reasonably predictable for any particular vector type except those particular ones in the art.

Applicant had amended the claims to limit the agent administration to those previously found enabled, however, due to the consideration of including general cytotoxins not encapsulated in liposomes, for the reasoning explained above, these claims are now rejected for any form of administration. Further, while some of these may be selectively cytotoxic to macrophages, the form of administration and amounts utilized is important, as indicated in e.g., Selgrade, et al. (1974) Infection and Immunity, 1383-90. However, there appears to be no indication in Applicant's specification to check the dosage and form of administration accordingly, much less any specific reference to such compound. Hence, the Artisan would have to perform undue experimentation to further determine which compounds through which method of administration affect the method, as stated above.

Further, with regard to each reference cited to demonstrate that the various compounds may be used to affect kupffer cell function, the following response is provided. With regard to the Lieber reference, Lieber teaches that the GdCl3 must be administered through the tailvein, which is well known to cause delivery to the liver (p. 8799), however, other forms of administration may kill other cells rather than cause delivery to the liver. With regard to the Kolb-Bachofen reference, the silica is toxic to macrophages, but is administered in vitro to purified macrophages (e.g., ABSTRACT), and hence, it would be undue experimentation to find the forms of administration and levels of compound required to produce the same effect on only kupffer cells in vitro. With regard to the Selgrade reference, outside of the method of delivery and levels of delivery, it would be undue experimentation to determine those other methods that work, with the amounts required. With regard to Rubin, the carrageen is not known to be selectively toxic, but through particular administration at particular levels, is toxic to kupffer cells, however, such does not enable any form of administration at any level – moreover, the implication of blocking uptake is there, but it is a cytotoxin, as also referenced in the text (the citation to Djeu, and Djeu's title). Hence, Rubin is a cytotoxin, not an agent that selectively precludes uptake by kupffer cells. With regard to Brunner, thorium dioxide is also a cytotoxin, and similarly subject to limitations in forms of delivery and amounts to deliver. With regard to Zenliman, it is clear that the methods of administration are limited by the amount of ricin used, and applicant has not limited the claims in such a manner (e.g., ABSTRACT). With regard to Cai, while Cai demonstrates less non-specific phagocytosis, as is clear above, such would not work for any particular vector with a specific form of entry into the cells. With regard to Rentsch, such appears to be covered by the other articles. Overall, Applicant appears to be

claiming mechanisms already known in the art, or at least obvious, i.e., killing kupffer cells or inhibiting their ability to uptake viral vectors to reduce their filtration of viral vectors. However, such self-determined invention is inconsistent with the disclosure of adenoviral vectors to inhibit uptake of further viral vectors. Further, these newly-presented articles appear to be Applicant's first discovery of this art, rather than a possessed genera, as no mention is made in the specification of the wide range of compounds used. To wit, while broadly stating "particulate matter" and specifically stating adenoviruses (p. 15), no mention is made that the Art demonstrates many such compounds, much less any specific examples which are not adenoviral vectors. Therefore, it appears to be that Applicant is now attempting to claim the liposomes and other compounds known in the art, having just discovered them. In fact, silicons are taught to be preferably inert carriers, and not agents of the invention (p. 18). Hence, the disclosure does not appear to be commensurate with that subject matter claimed in such a manner to be reasonably predictable for its breadth.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

In light of Applicant's amendments, the rejections of Claims 37, 39, 41-42, 44-46 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,025,195 to Sandig, et al., and Wolff, et al. (1997) J. Virol., 71(1): 624-29, is withdrawn.

To wit, the Art does not teach or suggest administration of these compounds in less than 2 hours before administering the viral vector. Moreover, the Art demonstrates the importance of checking to see when the kupffer cells no longer have the ability to uptake the viral vector (e.g., van Til, et al. (2005) Molec. Therap., 11(1): 26-34, p. 27, col. 2, paragraphs 2-5). Hence, it was not obvious to administer the viral vector so soon after or commensurate with the agent.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 52 is rejected under 35 U.S.C. 102(b) as being anticipated by US Pat. No. 6,001,557 to Wilson et al.

With regard to Claim 52, Wilson teaches a composition comprising two adenoviral vectors (e.g., Claim 1).

With regard to Claim 53, these vector compositions may be in the form of viral particles (e.g., EXAMPLES; Claim 1).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 38, 43, and 52-54 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 6,730,507 to Graham, et al.

With regard to Claims 52-53, Graham teaches compositions comprising two adenoviral vectors (e.g., Claims 1-3 and 5-6). Further, such adenoviral vectors are taught as particles (e.g., ABSTRACT), and the adenoviral vectors are taught to be used for therapeutic transgene expression (e.g., col. 12, paragraph 2), and hence would necessarily comprise the transgene in operable linkage with a promoter.

With regard to Claim 1, Graham teaches sequential administrations of adenoviral vectors by intravenous injection, which produces higher levels of transfection, and hence, higher levels of expression of the therapeutic transgene (EXAMPLE 6; col. 12, paragraph 2).

With regard to Claim 38, the vectors are adenoviral vectors (e.g., abstract).

With regard to Claim 43, at least IV administration is taught (e.g., EXAMPLE 6).

With regard to Claim 54, at least one vector may be replication defective (e.g., Claim 1).

It is noted that Graham does not teach any effect on Kupffer cells, but Graham performs the method steps with the required structure, and hence, Graham anticipates the claims, and therefore must also achieve the same result.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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